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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,668	05/06/1999	JONATHAN M. GERSHONI	27/135	1117

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,668	GERSHONI ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *144-156,159-170,177,179 and 183-194* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *144-156,159-170,177,179 and 183-194* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 28, 2004 has been entered.

Status

2. Claims 144-156, 159-170, 177, 179 and 183-194 are pending.

Claims 144-156, 159-170, 177, 179 and 183-194 are rejected.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 144-156, 159-170, 177, 179 and 183-194 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

Here, several of the limitations added to several different claims are apparently new matter.

The first limitation at issue is in claim 144 and was added in the afterfinal amendment which was not entered. The limitation states "such that any oligonucleotide any other in the library can ligate with oligonucleotide in the library". This limitation also appears in claim 159. The applicant did not cite any basis for this limitation in the response. A careful review by the examiner of the specification, particularly in example 5 which is the only part of the specification that deals with the claimed invention, failed to identify any support for this new limitation.

The second limitation is in claim 183 and 186 and was added in the June 28, 2004 amendment. The limitation states "wherein said providing and creating steps are accomplished such that none of the oligonucleotides created thereby encode said original single biological unit". Here again, the applicant did not cite any basis for this limitation in the response. The examiner also reviewed the specification for this limitation, again particularly in example 5 since this is the only part of the specification that deals with the claimed invention. This review failed to identify any support for this new limitation.

The third limitation is in claim 184, not previously examined since it was added in the June 28, 2004 amendment. The limitation states a "single definable sequence". The applicant argued that this has basis because cleavage of a genome must inherently result in a "single definable sequence". This statement is not correct since many genes have duplications, pseudogenes, or in the case of antibodies, for example, significant alternate splicing abilities. So the phrase is not inherent since it does not necessarily result from the method steps. With regard to this limitation, the absence of basis is significant because the term is also indefinite, since it is unclear what constitutes a "single definable sequence" and there is no definition or support in the specification to clarify the meaning of the term.

Since no basis has been found to support the new claim limitations in the specification, these claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 112

5. Claims 184-185 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the term "single definable sequence". As noted in the new matter rejection above, this term has no apparent basis in the specification. Applicant, in the response, attempts to define the term to distinguish "single biological unit" by adding this phrase and suggests that it requires a particular sequence. However, since many genes have duplications, pseudogenes, or in the case

of antibodies, for example, significant alternate splicing abilities, it is unclear what constitutes a "single definable sequence".

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 144-146, 148-151, 154, 155, 156, 159-161, 163-165, 168-170, 177, 179 and 183-194 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huse et al (Science, 1989, 246: 1275-1281) in view of Miyota et al (WO 98/05764).

Huse et al disclose a method (of claim 144) of identifying and producing a peptide which interacts with a ligand which interacts with a discontinuous epitope of a single biological unit comprising:

(a) providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. antibody) (see page 1277, column 2, where a plurality of antibody DNA fragments are used)

(b) creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments (see page 1277, column 2, where there is a random ligation event),

(c) inserting each of said oligonucleotides into an expression system (i.e. phage) (see page 1277, column 2, where the oligonucleotides are inserted into phage expression vectors),

(d) expressing the peptides encoded by the oligonucleotides (see page 1278, column 2, where the libraries were expressed);

(e) screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen) (see page 1278, column 2, where the libraries were screened for binding to a ligand);

(f) identifying the peptide (see page 1278, column 2, and page 1279, column 1, where the particular peptide was isolated and characterized by ELIZA) and

(g) producing the identified peptide (page 1279, column 1).

Regarding Claim 145, Huse et al disclose the method wherein step (a) comprises cutting said DNA sequence to form said plurality of DNA fragments (page 1278, left column, first full paragraph).

Regarding Claim 146, Huse et al disclose the method wherein said cutting is accomplished enzymatically i.e. restriction digestion (page 1278, left column, first full paragraph).

Regarding Claim 149, Huse et al disclose the method wherein step (b) comprises randomly ligating said plurality of DNA fragments to form at least one ligated fragment and at least partially digesting the ligated fragment to form said library i.e. the light chain fragments and heavy chain fragments are each randomly ligated into vectors and then digested (page 1277, right column, last three lines-page 1278, first three lines).

Regarding Claim 150, Huse et al disclose the method wherein said expression system comprises a plurality of bacteria and step (c) comprises inserting one of said library into each of said plurality of bacteria (page 1278, left column, first full paragraph).

Regarding Claim 151, Huse et al disclose the method wherein said expression system comprises a plurality of phage and step (c) comprises inserting one of said library into each of said plurality of phage (page 1278, left column, first full paragraph).

Regarding Claim 156, Huse et al disclose the method wherein the single biological unit is two or more proteins which interact to form a complex i.e. the single biological unit is a light chain and a heavy chain and the light and heavy chain interact to form an antibody complex (Abstract).

Regarding Claim 159, Huse et al disclose a method of preparing a library of peptides comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. Fab antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for

interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide (page 1277, right column, first full paragraph and Fig. 1; and page 1278, left column, first full paragraph).

Regarding Claim 160, Huse et al disclose the method wherein step (a) comprises cutting said DNA sequence to form said plurality of DNA fragments (page 1278, left column, first full paragraph).

Regarding Claim 161, Huse et al disclose the method wherein said cutting is accomplished enzymatically i.e. restriction digestion (page 1278, left column, first full paragraph).

Regarding Claim 163, Huse et al disclose the method wherein step (b) comprises randomly ligating said plurality of DNA fragments to form at least one ligated fragment and at least partially digesting the ligated fragment to form said library i.e. the light chain fragments and heavy chain fragments were each randomly ligated into vectors and then digested (page 1277, right column, last three lines-page 1278, first three lines).

Regarding Claim 164, Huse et al disclose the method wherein said expression system comprises a plurality of bacteria and step (c) comprises inserting one of said library into each of said plurality of bacteria (page 1278, left column, first full paragraph).

Regarding Claim 165, Huse et al disclose the method wherein said expression system comprises a plurality of phage and step (c) comprises inserting one of said library into each of said plurality of phage (page 1278, left column, first full paragraph).

Regarding Claim 169, Huse et al disclose the method wherein the single biological unit is a protein i.e. the single biological unit is an antibody and the fragments provide in (a) are fragments of the antibody (Abstract).

Regarding Claim 170, Huse et al disclose the method wherein the single biological unit is two or more proteins which interact to form a complex i.e. the single biological unit is a light chain and a heavy chain which interact to form an antibody complex (Abstract).

However, while Huse et al discloses applying the method to antibodies, Huse does not teach two elements. Huse does not clearly teach fragments which are randomly ligated such that any oligonucleotide can ligate with any other oligonucleotide in the library. Huse also does not teach a "single definable sequence", which for purposes of this rejection is treated as a single gene.

Miyota teaches a shuffling method in which sequences from a single gene, and in fact, a single particular sequence of a gene, are used (see page 24, example 1, where the API21 protease sequence is used and page 5, lines 8-10, where Miyota states that the pool can comprise "one or more genes" clearly indicating the use of a single gene) (addressing the new limitation of claims 184-186 and 192-194).

Miyota further teaches fragments which are randomly ligated such that any oligonucleotide can ligate with any other oligonucleotide in the library (see page 25, line 20 to page 26, line 6 where Miyota ligates the three blocks in any order. Miyota further expressly teaches this notion in stating "For example, when a gene is divided into 5 blocks, a1, a2, a3, a4 and a5, it is desirable that the nucleic acid pool obtained covers

substantially all different combinations each comprised of these 5 blocks (see page 12, line 27 to page 13, line 3)."

With regard to claims 177 and 179, Miyota expressly teaches fragments which are 45 nucleotides in length (see page 24, oligo 2) which is "about 50" base pairs.

With regard to claims 187-190, Miyota clarifies that every possible ligation product is desired in the next paragraph on page 13 as shown by the factorial language. Since Applicant is performing the same ligation, the same result will occur. To the extent that the original biological single unit will recur in Miyota, the same will occur in Applicant's method of ligation of every element to every other element.

With regard to claim 148, Miyota teaches synthesis of the DNA fragments (see example 1).

With regard to claims 154, 168, Miyota teaches the use of yeast as expression systems, where yeast are eukaryotic (see page 22, line 24).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Huse to apply the analysis to a "single definable sequence" wherein fragments are randomly ligated such that any oligonucleotide can ligate with any other oligonucleotide in the library since Miyota teaches that "the nucleic acid pool as obtained by shuffling a gene according to the present invention thus can cover such an extremely large number of nucleic acid molecules having different base sequences, each of which is different from the base sequence of the original gene (see page 13, lines 15-19)." So an ordinary practitioner would have been motivated to combine the method of Huse and Miyota and use the

random ligation method of Miyota in order to obtain a large and diverse library. Further, Miyota exemplifies application of the method to a single sequence (see example 1) and teaches and suggests its use on a "single definable sequence" however interpreted. Further, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the enzyme digestion of Huse et al with the methods of shuffling as taught by Miyota in order to obtain a complete set of shuffled genes with different base sequences than the original to yield a very diverse library for efficient and effective screening.

9. Claims 147 and 162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huse et al (Science, 1989, 246: 1275-1281) in view of Miyota et al (WO 98/05764) and further in view of Stemmer (U.S. Patent No. 5,811,238, filed 30 November 1995).

Huse in view of Miyota teach the limitations of claims 144-146, 148-151, 154, 155, 156, 159-165, and 169-170 as discussed above. Huse in view of Miyota do not teach the use of mechanical shearing.

Huse in view of Miyota do not teach cutting of the nucleic acid which is accomplished by mechanically cutting.

However, mechanical cutting of DNA was well know in the art at the time the claimed invention was made as taught by Stemmer et al. who teach a similar method of identifying and producing a peptide. Specifically, Stemmer et al teach the similar method comprising providing a plurality of DNA fragments which appear in a DNA sequence encoding a single biological unit (i.e. antibody); creating a library of oligonucleotides by randomly rearranging said fragments (i.e. shuffling); inserting the

oligonucleotides into an expression system; expressing and screening the expressed peptide (Column 5, lines 23-50) wherein the fragments are provided by mechanically cutting (Column 17, lines 30-35).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the enzyme digestion of Huse et al in view of Miyota with the mechanical shearing as taught by Stemmer et al to thereby eliminate the time and labor involved with DNA digestion and DNA purification following digestion for the obvious benefit of economy of time and labor.

10. Claims 152, 153, 166 and 167 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huse et al (Science, 1989, 246: 1275-1281) in view of Miyota et al (WO 98/05764) and further in view of Marks et al (The Journal of Biological Chemistry, 1992, 267(23): 16007-16010).

Huse in view of Miyota teach the limitations of claims 144-146, 148-151, 154, 155, 156, 159-165, and 169-170 as discussed above. Huse in view of Miyota do not teach that the oligonucleotides are cloned into phage genes coding for a coat protein.

Marks et al teach a similar method comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide

wherein the oligonucleotides are inserted into said phage by cloning (page 16008, Fig 1 and 2) wherein the said oligonucleotides are inserted into phage genes coding for a coat protein and wherein said coat protein is pIII or pVIII (page 16008, Fig. 2). Additionally, Marks et al teach that by inserting the oligonucleotide in to the coat proteins (e.g. pIII or pVIII) multiple antibodies are displayed on each phage providing higher binding avidity thereby maintaining antibody-antigen binding during washing even for the lower-affinity binding reactions (page 16009, left column, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the phage in the method of Huse et al in view of Miyota by inserting the oligonucleotide in to either the pIII or pVIII coat protein of filamentous phage as taught by Marks et al to thereby express multiple antibodies on each phage and increase binding avidity thereby maintaining antibody-antigen binding during washing and selection steps for the expected benefit of obtaining even lower-affinity binding reactions as taught by Marks et al (page 16009, left column, first paragraph) and thereby produce a more complete library as desired.

Response to Arguments

11. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
8/6/04